AMENDMENT

In the Claims:

Please amend claims 30 and 32-33 as follows, without prejudice to Applicants' right to pursue claims of the original scope in a duly filed continuing application:

30. [THREE TIMES AMENDED] A method of [~~modulating~~] interfering with interaction between a bone marrow stromal cell ~~expressing~~ VCAM-1 and a hemopoietic precursor [an immature ~~bone~~ marrow] cell which comprises administering an antibody to VCAM-1 ~~in~~ an amount effective to decrease VCAM-1-mediated adhesion between ~~the~~ bone marrow stromal cell and the hemopoietic precursor [bone marrow] cell.

32. [AMENDED] The method of claim 30 wherein the ~~hemopoietic~~ precursor [bone marrow] cell expresses CD34 ~~antigen~~.

33. [~~AMENDED~~] The method of claim 30 wherein the hemopoietic precursor [bone marrow] cell is a stem cell or a progenitor cell.

REMARKS

I. Preliminary Remarks

For the Examiner's convenience, a copy of currently pending claims 30-33 as amended is attached hereto as Exhibit A.

II. The Claimed Subject Matter

Claims 30-33 as amended are directed to use of an antibody that binds to vascular cell adhesion molecule-1 (VCAM-1), in methods directly relating to Applicants' discovery that bone marrow stromal cells express VCAM-1 and that VCAM-1 mediates adhesion between bone marrow stromal cells and hemopoietic precursor cells, especially those bearing the CD34 antigen. A representative embodiment of such an antibody that binds to VCAM-1 and that possesses the ability to block VCAM-1-mediated intercellular interactions is the 6G10 monoclonal antibody produced by hybridoma ATCC No. HB 10519.

III. The Outstanding Rejections

Claims 30-31 were rejected under 35 U.S.C. §112, first paragraph, for purportedly lacking written descriptive support in the specification. It was the Examiner's position that there did not appear to be support for the language "methods of modulating interaction" or the term "immature."

Claims 30 and 32-33 were rejected under 35 U.S.C. §112, first paragraph as assertedly lacking enablement for the full scope of the claims. It was the Examiner's position that the specification, while enabling for antibodies with the antigen-binding specificity of 6G10, does not reasonably enable any other VCAM-1-specific antibodies.

Claims 30-33 were rejected under 35 U.S.C. §112, first and second paragraphs for asserted indefiniteness in their recitation of the terms "modulating," "bone marrow stromal cell" and "immature bone marrow cell."

The claims were deemed to be free of the prior art.

Claims 30-33 were also provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 21-24 of co-pending application U.S. Serial No. 08/486,480.

IV. Patentability Arguments

A. The Rejection of Claims 30-31 Under 35 U.S.C. §112, First Paragraph

Claims 30-31 were rejected under 35 U.S.C. §112, first paragraph, for purportedly lacking written descriptive support in the specification. It was the Examiner's position that there did not appear to be support for the language "methods of modulating interaction" or the term "immature" (used in relation to bone marrow cells). This rejection may properly be withdrawn in light of the amendments to claim 30 that replace "modulating interaction" with "interfering with the interaction," and that also replace "immature bone marrow cell" with "hemopoietic precursor cell."

The term "modulating" has been replaced with "interfering" to address the Examiner's concerns regarding indefiniteness, as discussed *infra* in section C. Support is found throughout the specification for the concept of "interfering" with cell-cell interaction using monoclonal antibodies (mAbs) that bind to cellular adhesion molecules (CAMs) expressed by the cells. For example, the Summary of the Invention at page 4, lines 11-16 notes that contemplated binding partners, of which a representative embodiment is the 6G10 mAb, are preferably characterized by the ability to block lymphocyte binding to endothelial cells (which express VCAM-1) and to bind human VCAM-1 and bone marrow stromal cells. Example 4 notes at page 14, lines 28-32 that adhesion can be blocked by antibodies known to interfere with cell-cell interactions mediated by CAMs. Finally, Example 5 teaches at page 17, lines 24-33 that VCAM-1

(the CAM recognized by mAb 6G10) mediates adhesive interactions within the bone marrow between hemopoietic cells and stromal elements. Moreover, the Declaration of Beverly J. Torok-Storb, Ph.D., Under 37 C.F.R. §1.132 (Exhibit C to Applicants' previous paper no. 20 filed December 26, 1995) states that one of ordinary skill in the art, after being informed of the discovery of VCAM-1 expression on bone marrow stromal cells and their involvement in mediating adhesive interactions between hemopoietic cells and stromal elements, would have understood from the disclosure in the application that a clear therapeutic benefit of administering anti-VCAM-1 antibody to decrease adhesion of bone marrow cells to bone marrow stromal cells would be the interruption of progenitor/stroma binding.

The term "immature bone marrow cell" has been replaced with "hemopoietic precursor cell," also to address the Examiner's concerns regarding indefiniteness, as discussed *infra* in section C. Support is found in the specification at page 16, lines 36-37 and at page 17, lines 24-33.

This rejection under 35 U.S.C. §112, first paragraph, is therefore mooted by amendment of the claim language to which the Examiner objected.

B. The Rejection of Claims 30 and 32-33 Under 35 U.S.C. §112, First Paragraph

Claims 30 and 32-33 were rejected under 35 U.S.C. §112, first paragraph as assertedly lacking enablement for the full scope of the claims. It was the Examiner's position that the specification, while enabling for antibodies with the antigen-binding specificity of 6G10, does not reasonably enable any other VCAM-1-specific antibodies. This rejection may properly be withdrawn because the cited evidence of record shows that other anti-VCAM-1 antibodies decrease VCAM-1-mediated adhesive interactions between

hemopoietic cells and bone marrow stromal cells, and because no undue experimentation is required to produce additional VCAM-1-specific antibodies and to screen them for their ability to interfere with such adhesive interactions.

The Examiner's position that not all VCAM-1-specific antibodies were enabled was based on three assertions: (1) that the specification discloses in Example 5 that another VCAM-1-specific antibody (4B9) does not bind significantly to human bone marrow stroma, (2) that Simmons et al., *Blood, 80*:388-395 (1992) teaches that the anti-VCAM-1 antibody 6G10 did not block the binding of hemopoietic progenitors to marrow stroma, and (3) that Liesveld et al., *Blood, 81*:112-121 (1993) teaches that antibodies to VCAM-1, VLA-4α or other VLA integrins do not completely inhibit myeloid progenitor adhesion to marrow stroma.

With regard to the first assertion, despite the suggestion in the specification that the anti-VCAM-1 antibody 4B9 does not bind significantly to human bone marrow stroma, the Liesveld paper shows (at page 116, first col. and at page 117, Figure 4A) that in fact antibody 4B9 *does* bind to marrow stroma and was able to partially inhibit binding of a myeloblastic cell line to marrow stroma.

With regard to the second assertion, the Simmons paper reports (at page 390, second col.) that in fact, the anti-VCAM-1 antibody 6G10 *did effectively block adhesion* of hemopoietic cells to bone marrow stroma:

> [Antibody] 6G10 *inhibited the adhesion of both classes of progenitors* [granulocyte-macrophage colony-forming cells (CFU-GM) and erythroid progenitors (BFU-E)] to cytokine-treated stromal cells by *up to 90%* relative to that seen with isotype-matched control MoAbs. Significantly, 6G10 *also effectively blocked binding of progenitors to uninduced stromal cells* . . . [Emphasis added.]

With regard to the third assertion, the Liesveld paper shows that antibody 4B9 was able to partially inhibit binding of the myeloblastic cell line KG1a to bone marrow stroma, and concludes that VCAM-1 may participate in leukemic blast adhesion as the ligand for VLA-4. Liesveld et al. also state at page 118 (2nd col.) that:

> Such an [VCAM-1-mediated] interaction has also been noted for binding of lymphocyte or lymphocyte progenitors to endothelial cells, to murine marrow stromal cells, or to human marrow fibroblasts expressing VCAM-1, and, more recently, for adhesion of myeloid and erythroid progenitors to marrow stromal cells. [Cites omitted.]

Thus, the Simmons and Liesveld papers teach that even if complete (*i.e.*, 100%) blocking is not always obtainable, partial blocking of adhesion (*i.e.*, a decrease in adhesion) to bone marrow stroma is observed for at least two anti-VCAM-1 antibodies. Considering that the claims do not require complete blocking of VCAM-1-mediated adhesion, but merely address a decrease in VCAM-1-mediated adhesion, the evidence considered by the Examiner therefore fully supports enablement of the full scope of the claims.

Even if it were true that not all VCAM-1 antibodies are useful for interfering with the adhesive interaction mediated by VCAM-1 expressed on bone marrow stromal cells, it would require no more than routine experimentation to identify the antibodies that are useful. According to *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. . ." Under *Wands*, the factors to be considered in determining undue experimentation include (1) the quantity of experimentation, (2) the amount of direction or guidance presented, (3)

the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the art, and (8) the breadth of the claims.

In this case, the nature of the invention is the use of antibodies to a cellular adhesion molecule (CAM), VCAM-1, in methods for interfering with adhesive interactions involving VCAM-1. The state of the prior art was such that numerous antibodies to other CAMs were known to have the ability to interfere with intercellular interactions involving those respective CAMs, and the skill of those in the art was relatively high. Unlike methods for treating a particular disease, the methods here are directed to decreasing the adhesive interaction mediated by VCAM-1, an effect that is relatively highly predictable. The specification discloses at least one working example of an antibody, 6G10, that functions in the claimed method. The quantity of experimentation required to produce additional anti-VCAM-1 antibodies is not undue (see *Wands*), and it is well within the skill of the ordinary worker to screen these antibodies for inhibition of VCAM-1-mediated adhesion to human bone marrow stroma.

The Applicants believe that there is considerable analogy between the fact situations in this case and in Example J of the U.S.P.T.O. Training Materials for Enablement (Fall, 1996), in which it was considered "reasonable not to make any enablement or scope rejection" to claims including a method for the treatment of diseases characterized by selectin-mediated cellular adhesion. In Example J, some of the disclosed compounds inhibited selectin-mediated cellular adhesion, but some of the compounds meeting the structural limitations of the claims failed to inhibit P-selectin-mediated cellular adhesion. Nevertheless, "it would be reasonable to conclude that while the scope of the claims would encompass non-operative embodiments, the experimentation needed

to determine the operative embodiments and to use those embodiments would not be undue."

Therefore, the Applicants respectfully submit that this rejection under 35 U.S.C. §112, first paragraph, may properly be withdrawn because the cited evidence of record supports enablement of the full scope of claims drawn to interfering with VCAM-1-mediated adhesive interactions, and because no undue experimentation is required to identify additional useful VCAM-1-specific antibodies.

C. The Rejection of Claims 30-33 Under 35 U.S.C. §112, Second Paragraph

Claims 30-33 were rejected under 35 U.S.C. §112, first and second paragraphs for asserted indefiniteness in their recitation of the terms "modulating," "bone marrow stromal cell" and "immature bone marrow cell." This rejection may properly be withdrawn in light of the amendments to claim 30 to more clearly describe the type of modulation envisioned and the cells involved.

The Examiner suggested that the method claims be redrafted as "inhibition or other appropriate terms that relate to the type of modulation." In response, Applicants have rephrased the term "modulating" as "interfering" with cell-cell interaction. Support in the specification is indicated *supra* in section A.

The Examiner also suggested that the claims be amended to "distinguish between stromal cells and hemopoietic cells." In response, the Applicants have more clearly identified the cells involved in the adhesive interaction by replacing the term "bone marrow cell" with "hemopoietic precursor cell" and by specifying that the bone marrow stromal cell expresses VCAM-1. Support in the specification for the term "hemopoietic precursor cell" is indicated *supra* in section A. Support for the expression

of VCAM-1 by the stromal cell is found, *e.g.*, at page 4, lines 11-16 and at page 17, lines 24-33 of the specification.

D. The Rejection Under the Doctrine of Obviousness-Type Double Patenting

Claims 30-33 were also provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 21-24 of co-pending application U.S. Serial No. 08/486,480. This provisional rejection is mooted by the cancellation of claims 21-24, which are commensurate in scope with the present claims, by a concurrently filed amendment in U.S. Serial No. 08/486,480.

CONCLUSION

In light of the foregoing amendments and remarks, it is believed that claims 30-33 are now in condition for allowance, and early notice thereof is solicited.

Respectfully submitted,

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